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**Childhood trauma and mixed episodes are associated with poor response to lithium in bipolar disorders**

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## Childhood trauma and mixed episodes are associated with poor response to lithium in bipolar disorders

Running title: childhood trauma and response to lithium

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**Abstract**

**Objectives:** Reliable predictors of response to lithium are still lacking in bipolar disorders (BD). However, childhood trauma has been hypothesized to be associated with poor response to lithium.

**Methods:** We included 148 patients with BD, euthymic when retrospectively and clinically assessed for response to lithium and childhood trauma using reliable scales.

**Results:** According to the “Alda scale”, the sample consisted in 20.3% of excellent responders, 49.3% of partial responders and 30.4% of non-responders to lithium. A higher level of physical abuse significantly correlated with a lower level of response to lithium ( $p=0.009$ ). As compared to patients not exposed to any abuse, patients with at least two trauma abuses (emotional, physical or sexual) were more at risk of belonging to the non-responders group ( $OR=4.91$  95CI(1.01-27.02)). Among investigated clinical variables, lifetime presence of mixed episodes and alcohol misuse were associated to non-response to lithium. Multivariate analyses demonstrated that physical abuse and mixed episodes were independently associated with poor response to lithium ( $p=0.005$  and  $p=0.013$  respectively).

**Conclusions:** Childhood physical abuse might be involved in a poor future response to lithium prophylaxis, this effect being independent of the association between clinical expression of BD and poor response to lithium.

**Key words**

Bipolar disorder, lithium response, childhood trauma, physical abuse, mixed episodes, alcohol misuse

**Significant outcomes**

A higher level of physical abuse significantly correlated with a lower level of response to lithium.

Patients with high exposure to trauma had a 4-fold increased risk of being non-responders to lithium.

History of physical abuse and mixed episodes were independently associated with poor response to lithium.

**Limitations**

The sample size was relatively small.

All assessments were made retrospectively.

The study was cross-sectional and causality cannot be definitively determined.

## Introduction

Predicting response to lithium in Bipolar Disorders (BD) is challenging but crucial for moving towards more personalized medicine (1). This is because, not all patients receiving lithium carbonate for at least two cumulative years of treatment will display improvement in the frequency and/or severity of mood recurrences. For example, by reviewing charts of 120 patients with BD and using the **Retrospective Criteria of Long-Term Treatment Response in Research Subjects with Bipolar Disorder (also referred as the “Alda scale”)** (2), Garnham and colleagues identified that the highest rate of complete response to lithium is observed for only approximately 30% of patients (3). Within the ConLiGen consortium (The International Consortium on Lithium Genetics), Manchia and colleagues have performed a study including 1,308 patients with BD from 29 sites and assessing response to lithium with the “Alda scale” (4). Mixture modelling of score distribution indicated three subpopulations (full responders, partial responders, non-responders) with around one-third of patients belonging to each groups.

Several variables related to BD clinical presentation have been extensively studied to identify those that would predict response to lithium when the treatment is first prescribed, although with disappointing results and a lack of consensus about robust predictors (5). In particular, Kleindienst et al. in 2005 used a meta-analytic approach to identify those predictive variables (6) and investigated forty-two potential clinical predictors. An episodic pattern sequence of mania-depression-interval and a late age at onset of BD predicted good response to lithium. A high number of previous hospitalizations, an episodic pattern sequence of depression-mania-interval, and continuous cycling predicted poor response to lithium. All the associations with these variables exhibited significant but small effect sizes, the larger effect size being observed for high number of hospitalizations. Another variable that is likely to predict good response to lithium is a history of good response in the patient's affected relatives, response to lithium being thus suggested as a familial trait (7, 8). Although it requires replications, patients who started lithium early during the course of the disorder were expected to have significantly increased rates of response to lithium as compared to patients starting lithium later (9). **Some medical conditions have also been suggested to predict or to be associated with poor response to lithium (10). This was particularly the case for obesity, insulin resistance or type 2 diabetes (11-13).**

Recently, studies have investigated the history of childhood traumatic events as a predictor of non-response to psychotropic drugs in psychiatry. Several studies have suggested an association between

early life adversity or childhood trauma and lower response or resistance to medication in depression in adults or adolescents (14-18). This issue has also been addressed in schizophrenia spectrum disorders with less convincing results (19). Only two studies have investigated such a hypothesis specifically in BD. Cakir et al. 2015 have used a sample of 135 patients with BD type I assessed for childhood trauma. Response to long-term treatment was determined from the records of life charts of the prospective follow-up project (20). They found no significant differences between good and poor response groups to long-term lithium treatment on childhood trauma scores. A study of 38 preschool-onset BD young patients who insufficiently responded to lithium monotherapy suggested that a history of sexual or physical abuse was a significant predictor of an inadequate response to lithium monotherapy, then requiring augmentation with risperidone (21).

Interestingly, childhood trauma has been associated with several clinical variables that are likely to be associated with poor lithium response such as early onset, mixed features, rapid cycling, and substance misuse (22-26). Moreover, childhood trauma has been associated with numerous medical conditions such as obesity (27, 28), cardiovascular diseases, asthma, gastric ulcers, migraine, arthritis (29), metabolic risk markers (30) or diabetes (31). Some of these somatic conditions were in turn associated with poor response to lithium as mentioned above. This means that patients with BD and childhood trauma might experience not only a more severe course of BD but also a greater burden due to associated medical conditions. Whether childhood trauma predisposes to poor response to lithium directly or through the occurrence of some clinical psychiatric manifestations or some associated medical conditions that predispose patients to resist to lithium prophylaxis, remains an underexplored issue. We have highlighted this issue as a gap in research in a recent review (22).

The aim of this study was to investigate the association between response to lithium, clinical characteristics of the disorder and childhood trauma in patients with BD.

## Material and methods

### Sample selection

The sample consisted of euthymic patients with BD type I, II or not otherwise specified (NOS) who were recruited from three academic psychiatric departments in France (Paris/Créteil, Bordeaux and Nancy). Patient inclusion criteria for this study were: aged over 18 years; having a diagnosis of BD according to DSM-IV criteria (32); being Caucasian; clinically euthymic at the time of inclusion (i.e. having a Montgomery Asberg Depression Rating Scale score (33) and a Mania Rating Scale score (34)

below five, as well as no major mood episodes in the last three months); having completed the Childhood Trauma Questionnaire (35), and whose response to lithium has been assessed using the “Alda scale” (2).

Written informed consent was obtained from all participants. This study was approved by the French medical ethics committee (Comité de Protection des Personnes (CPP) - IDRCB2008\_AO1465\_50 VI—Pitié Salpêtrière 118-08) and carried out according to the approved guidelines.

### **Clinical variables related to BD**

Patients were interviewed using the French version (36) of the Diagnostic Interview for Genetic Studies (DIGS) (37), which provided lifetime DSM-IV axis I diagnoses (32). A set of variables was extracted from the DIGS to characterize the clinical expression of BD. The age at onset (AAO) of BD was determined retrospectively and was defined as the age at which a patient first met DSM-IV criteria for a major depressive or (hypo)manic episode according to the information collected with the DIGS. Polarity at onset of BD was defined as the polarity of the first episode (depressive polarity at onset in the case of a first major depressive episode *versus* manic polarity at onset in case of a first (hypo)manic or mixed first episode). Mixed episodes, suicide attempt and rapid cycling were recorded as present if they occurred at any point of the course of BD (lifetime presence). Substance (alcohol or cannabis) misuse was coded as present if the patient fulfilled the DSM-IV criteria for abuse or dependence to these substances at any moment of the course of BD (lifetime presence).

Misuses with other substances than alcohol or cannabis had a too low prevalence in our sample to be studied as such. We also studied the three more frequent comorbid anxiety disorders in our sample, i.e. panic disorder, social phobia and generalized anxiety disorder. Other anxiety disorders such as obsessive-compulsive disorder had a too low prevalence in our sample to be studied as such.

### **Assessments**

Childhood traumatic events were assessed using the Childhood Trauma Questionnaire (CTQ), a 28-item self-report questionnaire (35). The CTQ yields a total score and five subscale scores for emotional and physical neglects, as well as emotional, physical and sexual abuses. The CTQ total score was used as a continuous variable assessing trauma severity. Based on the cut-off values proposed by Bernstein and Fink (38), we used the scores for each subscale to determine the severity of each kind of trauma (absent/low, mild, moderate or severe). A trauma subtype was considered as present if at least of moderate or severe intensity. This allowed then to define the cumulative number of experienced trauma subtypes. In this study, we focussed on abuse types (emotional, physical and sexual) rather than types of neglect (emotional and physical). This was because we

demonstrated that the associations between childhood trauma and susceptibility to BD or a more severe clinical outcome seemed to be mainly driven by abuse rather than neglect (39, 40).

The “Alda scale” has been designed to retrospectively assess response to lithium (2). This scale quantifies the degree of improvement in the course of treatment (A criterion) expressed as a weighed against 5 factors (B criteria). The B criteria assessed the number of episodes before/off treatment (B1), the frequency of episodes before/off treatment (B2), the duration of the treatment (B3), the compliance during period(s) of stability (B4) and the use of additional medication during the period of stability (B5). A total score (TS) is then obtained by subtracting the B score from the A score. This enables to determine whether the observed improvement is either a result of the treatment, a spontaneous improvement or just an effect of additional medication. The “Alda scale” was scored for all patients by a trained psychiatrist (CPB). For most analyses, “Alda scale” scores were used as continuous variables to maximize the power of the study by avoiding any categorization of the scores. When it was relevant to calculate Odd Ratios (OR) and 95% Confidence Intervals (95CI), categorized scores were used to allow the comparisons of excellent (scores of 7 to 10), partial (scores from 2 to 6) and non-responders (scores of 0 or 1) based on the cut-offs validated by (4).

The inclusions of patients were performed between 2005 and 2010 (clinical assessment with the DIGS and completion of the CTQ). All Alda scales were then scored in 2012 using the clinical information collected between the onset of the disorder (first major mood episode identified using the DIGS) and the time at inclusion.

The response to other mood stabilizing treatments was not determined in this sample.

### Statistical analysis

Scores of the “Alda scale” were compared between groups using non parametric Wilcoxon rank tests, since the distribution of the “Alda scale” score did not fit a normal distribution (Kolmogorov-Smirnov test). Associations between categorical variables were tested using Chi-square tests and if appropriate exact tests of Fisher. Odd ratios (OR) were provided when relevant and given with the 95% Confidence Interval (CI) to quantify the magnitude and direction of any significant associations. Correlations between continuous variables were calculated using Spearman correlation tests. Multivariable stepwise ordinal logistic regression was used to test for the association between “Alda scale” categorized score (0: lithium non responders, 1: partial lithium responders, 2: excellent lithium responders) and continuous trauma scores after adjusting for potential confounding variables. All analyses were carried out using STATA version 13 software or the IBM SPSS Statistics version 21.



In that case of a clinical variable being associated to response to lithium, we performed a path analysis from childhood trauma score to response to lithium using the clinical variable as a potential mediator. The model examined both direct and indirect associations between the trauma score and the response to lithium. The model estimated indirect association through the mediator. A path diagram representation of the model was then drawn. The path-analysis was performed using MPLUS (41).

## Results

The sample consisted in 89 females and 59 males with a mean (SD) age at onset of 45.84 (12.25) years. Patients mainly suffered from BD type I or II (112 and 34 respectively) with only 2 patients suffering from BD NOS. According to “Alda scale” cut-offs, the sample consisted in 20.3% of excellent responders, 49.3% of partial responders and 30.4% of non-responders to lithium. 70% of the sample had at least two years of lithium treatment and 12% less than one year (“Alda scale” B3 criterion). Only 3% of patients were considered as poor adherent to lithium (“Alda scale” B4 criterion).

Mean (SD) CTQ total score was 41.12 (11.66) (range: 25-78). The frequencies of patients having experienced trauma of at least moderate severity were: 22.4% for emotional abuse, 7.5% for physical abuse and 17.8% for sexual abuse. Trauma subtypes could be cumulative corresponding to 52.1% of patients with no trauma, 24.3% with only one trauma subtype and 23.5% with at least two trauma subtypes.

First we used “Alda scale” total score and CTQ (sub)scores as continuous variables. We found a negative correlation between a higher level of physical abuse and a lower level of response to lithium (see table 1). This negative correlation was also observed when restricting the analysis only to those patients with at least 2 years of treatment with lithium ( $\rho = -0.21$   $p = 0.03$ ).

- insert table 1 here -

Regarding the cumulative number of trauma, there was a descending gradient of response to lithium from those having no trauma to those having one or two and more trauma subtypes (Linear-by-Linear Association test  $p = 0.014$ ), suggestive of a dose-effect. Specifically, as compared to patients not exposed to any trauma, patients with at least two trauma subtypes were more at risk of belonging to the non-responders group (OR=4.91 95CI(1.01-27.02), exact test  $p = 0.03$ ) (see figure 1).

- insert figure 1 here -

As shown in table 2, ~~only one clinical variable was associated with poor response to lithium in our sample.~~ those patients with lifetime history of mixed episodes had significantly lower “Alda scale” total score meaning that they responded less to lithium. Using categorized scores for the “Alda scale” yielded similar results, patients with mixed episodes were more likely to be non-responders *versus* excellent responders as compared to those without mixed episodes (OR=6.76 95CI(1.24-48.45); exact test  $p=0.01$ ). We found an association between a lower response to lithium and alcohol misuse, also with a trend for an association with rapid cycling. There was no correlation between “Alda scale” total score and age at onset (Spearman correlation test  $\rho=0.022$   $p=0.79$ ), nor with the duration of the illness (Spearman correlation test  $\rho=0.029$   $p=0.73$ ). None of the investigated anxiety disorders were associated with response to lithium.

- insert table 2 here -

We then performed a stepwise ordinal regression using the categorical response status on the “Alda scale” as the dependent variable, physical abuse score (continuous) and three following categorical clinical variables (lifetime presence *versus* absence): mixed episodes, rapid cycling and alcohol misuse as independent variables. We used 118 observations in the model since some data were missing for some variables. A likelihood ratio chi-square of 16.28 was observed ( $p=0.0003$ ), meaning that this model as a whole was statistically significant, as compared to the null model with no predictors. Only physical abuse ( $p=0.005$ ) and presence of mixed episodes ( $p=0.013$ ) were retained in the model and were found to be significantly associated with poor response to lithium (table 3). The results of the full model including the 4 independent variables are presented in Supplementary table 1.

- insert table 3 here -

We tested the ability of the model to correctly classify excellent ( $n=27$ ) *versus* non responders ( $n=37$ ) (Receiver Operating Characteristics). The Area Under the Curve is 0.75, which is considered to be fair. As a whole, 67% of cases were correctly classified (65% of non-responders and 70% of excellent responders).

Finally, the path analysis using physical abuse as the independent variable, “Alda scale” score as the dependent variable and lifetime presence of mixed episodes as a potential mediator suggested that there was a significant direct effect of physical abuse on “Alda scale” scores ( $p=0.02$ ) and that the indirect effect through mixed episodes was not significant ( $p=0.74$ ) (see supplementary figure 1).

## Discussion

In this study we found that poor response to lithium was independently associated with physical abuse and lifetime history of mixed episodes. This suggests that physical abuse does not mediate poor response to lithium through increased risk of mixed episodes, but rather by a direct effect.

We reported associations between poor response to lithium, mixed episodes and alcohol misuse with a trend for an association with rapid cycling. We did not replicate other previously reported results such as the association between age at onset and different levels of lithium response. Some negative or borderline significant results may be partly explained by the sample size of our study that was of reasonable size as compared to previous studies (two thirds of the studies reviewed by (6) included less than 100 patients). Only one study has previously reported association between a mixed index episode and subsequent response to lithium prophylaxis with borderline p value ( $p=0.06$ ) in a sample of 186 patients with BD (42).

We observed for the first time an association between physical abuse and poor response to lithium. This has not been reported by a recently published study (20). This study has a smaller sample size than ours ( $n=135$  patients with 92 of them receiving lithium) but similar criteria for euthymia and also used the CTQ for assessing childhood trauma. However, some methodological differences should be pointed out such as the definition of response to lithium, the prospective design of the study and the inclusion of patients with BD type 1 only. Further studies are thus required to confirm our observed associations. Further investigations of the association with other subtypes of trauma are also required. Indeed the close to zero correlation coefficient ( $r=-0.02$ ) between sexual abuse and “Alda scale” total score might indicate the genuine absence of association in our sample. However, the absence of association between emotional abuse and “Alda scale” total score might indicate a lack of power in our study ( $r=-0.13$   $p=0.12$ ). Research efforts should be then put to collecting trauma history when studying response to lithium or merging data within large consortia (4).

Given the design of the “Alda scale”, some issues can be raised on whether physical abuse is genuinely compromising the response to lithium and/or increases other features related to non-response. Indeed section A is a measure of improvement with lithium based on the reduction of the illness activity whereas part B includes mixed items about compliance during period(s) of stability (B4) and the use of additional medication during the period of stability (B5). The total score might thus be reduced given an increased B section score. Childhood trauma might lead to more additional medication prescriptions or reduced compliance through more complex presentation of the BD (43).

However, when looking more closely to sub-scores, physical abuse negatively correlated with part A score ( $\rho=-0.24$ ;  $p=0.003$ ), but not with part B score ( $\rho=0.007$ ;  $p=0.93$ ). Moreover, partial correlation between physical abuse and part A score remained significant when adjusting for part B score ( $\rho=-0.20$ ;  $p=0.016$ ). Clearly, this suggests that the deleterious effect of physical abuse mainly acts through a lack of reduction of the illness activity. This is in keeping of the increased number of depressive and manic episodes observed among patients with BD who have been exposed to childhood trauma (39).

The path-analysis suggested that the effect of physical abuse on response to lithium appeared not to be fully mediated by the increased presence of mixed episodes but to have deleterious effects on its own. This raises very promising hypothesis to be explored about the molecular mechanisms that might drive this effect. We can hypothesize that physical abuse impact on several biological pathways (related to inflammatory processes, neuroplasticity, circadian systems or premature ageing among others) (22), maybe such effect(s) not being fully counteracted by lithium salts, thus explaining why some bipolar patients who received lithium remained at high-risk for mood recurrences. For example some studies have shown that childhood trauma reduces BDNF mRNA blood levels among exposed schizophrenia spectrum disorders and BD (44, 45) and also modifies levels of numerous inflammatory markers in clinical and non-clinical populations (46-48) such as C Reactive Protein, Interleukine 6 or Tumor Necrosis Factor alpha (49). This has been proposed to create an imbalance between neuroplasticity and pro-inflammatory cytokines levels (50) with some increase in BDNF levels being a possible attempt to neutralize the negative effects of childhood trauma on the brain. Molecular hypotheses regarding the circadian system are also of great interest since the circadian system is targeted by lithium and modulates the biological responses to stressful environmental factors (51). Childhood trauma and other stress factors are also causal factors for the long-term reduction of telomere length (52, 53). This telomere length shortening is still discussed in BD (54) but would be counteracted by lithium (55). Therefore, childhood trauma might be associated with poor response to lithium through long-lasting biological consequences.

Childhood trauma also has been associated with long-term effects on prefrontal-limbic brain structures. For example, a recent meta-analysis in adults with a history of childhood trauma demonstrated that trauma cohorts exhibited smaller hippocampus and amygdala volumes bilaterally along with reduced grey matter in the right dorsolateral prefrontal cortex (56). In a sample of patients with BD and healthy controls, we found CTQ total scores to be negatively correlated with amygdala volumes, prefronto-limbic functional connectivity and uncinate fractional anisotropy (57).

Therefore, childhood trauma might alter the volume of and/or connectivity between brain areas that might be less sensitive to the potential effects of lithium salts.

Finally, BD is characterized by an altered sensitivity of the HPA axis (increased levels of cortisol (basal and post-dexamethasone) and ACTH) as demonstrated by recent meta-analyses and the authors have suggested that such an observation seems related to environmental risk factors, such as childhood trauma (58, 59). This modification of the sensitivity of the HPA axis might be related both to the vulnerability to BD but also to some associated medical conditions such as obesity, diabetes type 2 or insulin resistance that in turn would increase the likelihood of non-response to lithium (10-13). One plausible hypothesis to be further tested is that such medical conditions might influence the links between childhood trauma and poor response to lithium, possibly through alterations of several inflammatory markers or through the HPA axis. This will represent a new avenue for more research about the links between childhood trauma and response to lithium and should be investigated in future studies.

This study has several limitations. The sample size remains small (even though reasonable according to the available literature), which suggests that some false negative could not definitely be excluded. Assessments of clinical presentation of BD and of childhood trauma were done retrospectively which might have led to recall bias. The recording of lithium response was also made in a retrospective manner based on available information collected with the DIGS. Euthymia was one of the criteria to be included in the study; this might have oversampled patients for which stabilization is reachable and thus excluding more instable patients with both childhood trauma and poor response to lithium. Further studies including also patients with more acute or chronic symptoms might extend our findings. The selection of associated clinical variables and correlations with childhood trauma scores were performed using the “Alda scale” total score as a continuous variable, while the final regression model used three categories based on validated cut-offs (4). This was mainly due to the distribution of the “Alda scale” total score in our population, which is very similar to the one observed in Manchia et al. (4) (mixture of three Gaussian distributions). The non-normality of this distribution and the inability to transform properly the total score to fit a normal distribution prevented us from using it as a continuous variable in the regression analysis. Instead we used an ordinal regression that might reduce the statistical power to detect some of the associations. A detailed description of associated medical conditions was not available in our sample. As such, we were not able to describe whether such conditions might also mediate the links between childhood trauma and response to lithium in order to go beyond the associations that we reported with mixed episodes. As this was a

retrospective study and not a prospective one, we have to emphasize that causality between childhood trauma and response to lithium cannot be definitively determined. Finally, we have collected no information related to the response to other mood stabilizing agents. Therefore we cannot conclude whether the associations found here are specific to lithium or generalizable to other mood stabilizers (3).

## Conclusion

Childhood trauma might play a role in the non-response to lithium prophylaxis in BD. Physical abuse may be particularly involved, although our study suggested that emotional abuse would deserve further investigation in larger samples of patients. The association between physical abuse and poor response to lithium appeared to be independent of the association observed between poor response to lithium and mixed episodes. These results open a new avenue for exploring biological mechanisms of poor response to lithium that might be enhanced by the exposure to childhood trauma.

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**Conflict of interest**

None. The authors declare that they have no competing financial interests, or other interests that might be perceived to influence the results and discussion reported in this paper.

**Role of the authors**

BE wrote the first draft of the paper and is the scientific coordinator of the study. FB is the principal investigator of the study. CBP scored the "Alda scale" for the sample. PAG, CH, SG, JPK, MLe recruited or supervised the recruitment of patients. MLa performed the statistical analyses. AHY revised the last version of the paper. All the authors approved the submitted version of the paper.

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*Table 1: Spearman's correlation coefficients between “Alda scale” total score and CTQ (sub)scores*

|                          | CTQ total score |      | Emotional abuse |      | Physical abuse |              | Sexual abuse |      |
|--------------------------|-----------------|------|-----------------|------|----------------|--------------|--------------|------|
|                          | rho             | p    | rho             | p    | rho            | p            | rho          | p    |
| “Alda scale” total score | -0.15           | 0.07 | -0.13           | 0.12 | -0.21          | <b>0.009</b> | -0.02        | 0.85 |

CTQ: Childhood Trauma Questionnaire

Significant correlations are presented in bold.

**Figure 1: Percentage of excellent, partial and non-responders according to the number of trauma**

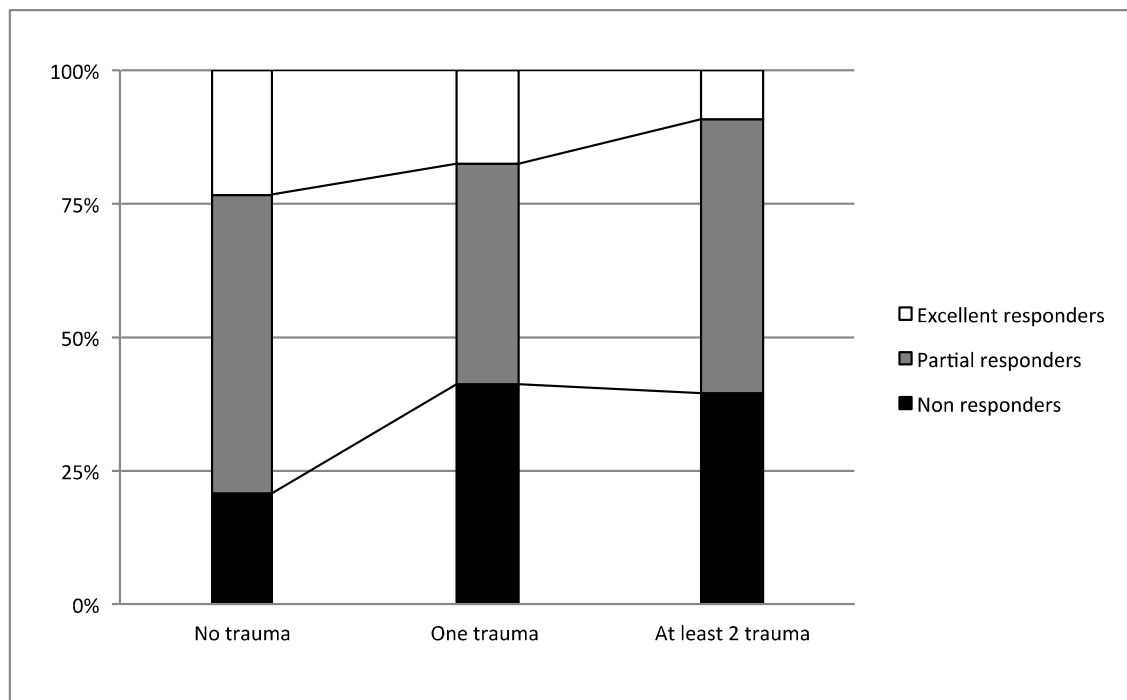


Table 2: Means (SD) for “Alda scale” score according to categorical clinical variables

| Clinical variables | Type                | N         | Mean SD (yes) | Mean SD (no) | p            |
|--------------------|---------------------|-----------|---------------|--------------|--------------|
| BD type            | I vs II             | 112 vs 34 | 3.59 (2.86)   | 3.85 (2.90)  | 0.56         |
| Polarity at onset  | Depressive vs Manic | 83 vs 63  | 3.42 (2.86)   | 3.95 (2.85)  | 0.28         |
| Rapid cycling      | Yes vs No           | 27 vs 110 | 2.78 (2.88)   | 3.91 (2.85)  | 0.071        |
| Mixed episodes     | Yes vs No           | 29 vs 101 | 2.48 (2.54)   | 4.09 (2.87)  | <b>0.007</b> |
| Suicide attempt    | Yes vs No           | 60 vs 84  | 3.90 (3.16)   | 3.59 (2.70)  | 0.65         |
| Alcohol misuse     | Yes vs No           | 23 vs 123 | 2.48 (2.48)   | 3.88 (2.89)  | <b>0.032</b> |
| Cannabis misuse    | Yes vs No           | 14 vs 132 | 3.43 (3.00)   | 3.68 (2.87)  | 0.77         |
| Panic disorder     | Yes vs No           | 38 vs 106 | 3.74 (2.68)   | 3.62 (2.93)  | 0.87         |
| Social phobia      | Yes vs No           | 20 vs 124 | 3.10 (2.90)   | 3.74 (2.85)  | 0.33         |
| GAD                | Yes vs No           | 10 vs 112 | 2.60 (3.17)   | 3.47 (2.82)  | 0.33         |

Note: Lower scores of the “Alda scale” indicate lower response to lithium.

N: number of patients with/without the clinical variable, SD: Standard Deviation, vs = versus.

Significant differences are presented in bold.

BD: Bipolar Disorder, GAD: Generalized Anxiety Disorder.

**Table 3: results of the ordinal stepwise regression analysis**

| Variables*            | OR    | Std. Err. | z     | P> z         | [95CI] |       |
|-----------------------|-------|-----------|-------|--------------|--------|-------|
| <b>Mixed episodes</b> | 0.33  | 0.15      | -2.48 | <b>0.013</b> | 0.14   | 0.79  |
| <b>Physical abuse</b> | 0.78  | 0.067     | -2.84 | <b>0.005</b> | 0.66   | 0.93  |
|                       |       |           |       |              |        |       |
| <b>/cut1</b>          | -2.73 | 0.59      |       |              | -3.89  | -1.56 |
| <b>/cut2</b>          | -0.33 | 0.54      |       |              | -1.39  | 0.73  |

OR: Odd Ratio, Std. Err.: Standard Error, CI: Confidence Interval

\* Categorical response to lithium as the dependent variable; physical abuse, mixed episodes, rapid cycling and alcohol misuse as the dependent variables

*Note: The results were displayed as proportional odds ratios. The odds of excellent response to lithium versus the combined partial and non-response was 0.33 lower in the presence of mixed episodes, given that all of the other variables in the model are held constant. For each unit increase of physical abuse, the odds of excellent response versus the combined partial and non-response was 0.78 lower, given that all of the other variables in the model are held constant.*

*Note: in the ordinal regression, the cut points shown at the bottom of the tables indicated where the latent variable was cut to make the three groups that we observed in our data. Note that this latent variable is continuous.*

Supplementary Table 1: results of the ordinal regression analysis (full model)

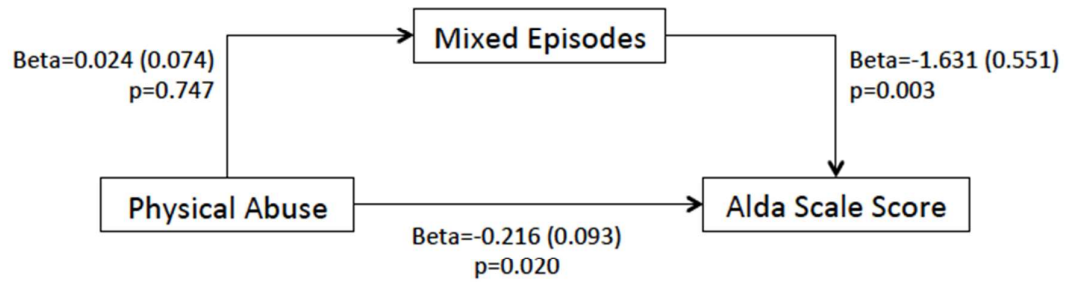
| Variables*     | OR    | Std. Err. | z     | P> z  | [95CI] |       |
|----------------|-------|-----------|-------|-------|--------|-------|
| Mixed episodes | 0.42  | 0.20      | -1.92 | 0.055 | 0.17   | 1.02  |
| Physical abuse | 0.78  | 0.07      | -2.88 | 0.004 | 0.66   | 0.92  |
| Alcohol misuse | 0.60  | 0.32      | -0.95 | 0.344 | 0.21   | 1.71  |
| Rapid cycling  | 0.52  | 0.26      | -1.32 | 0.188 | 0.20   | 1.37  |
|                |       |           |       |       |        |       |
| /cut1          | -2.96 | 0.62      |       |       | -4.17  | -1.75 |
| /cut2          | -0.50 | 0.55      |       |       | -1.58  | 0.58  |

OR: Odd Ratio, Std. Err.: Standard Error, CI: Confidence Interval

\* Categorical response to lithium as the dependent variable; physical abuse, mixed episodes, rapid cycling and alcohol misuse as the dependent variables

Supplementary figure 1:

Path analysis from Physical Abuse to Alda Scale Score : direct and indirect effects through Mixed Episodes



N=145

Indirect effect :  $\text{beta}=-0.039$  (0.121)  $p=0.746$